LEUCOCYTHEMIA:

An Essay,

TO WHICH WAS AWARDED THE BOYLSTON MEDICAL PRIZE

OF HARVARD UNIVERSITY FOR 1863.

BY

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ANIMA OMNIS CARNIS IN SANGUINE EST.

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1*st*, That this Board do not consider themselves as approving the doctrines contained in any of the dissertations to which premiums may be adjudged.

2*d*, That, in case of publication of a successful dissertation, the author to be considered as bound to print the above vote in connection therewith.

PREFACE.

A LARGE portion of the following Essay has been necessarily devoted to the difficult task of condensing into as small a compass as possible whatever is known in regard to the origin and formation of the cellular elements of the blood. While engaged in these studies, similar ones were pursued abroad; and Dr. WILLIAM ROBERTS communicated to the Royal Society, Feb. 10, 1863, some observations upon the appearances of the blood-corpuscles under the influence of solutions of magenta and tannin. An account of these experiments is given in the "London Quarterly Journal of Microscopical Science" for July, 1863; and figures also of the blood-corpuscles. About the time of his discovery, similar phenomena were noticed by the author of this Essay in pathological blood.

It may be interesting to know something more of the history of the two cases of leucocythemia which were then under the care of the author. The following account of the removal of the large glandular tumor from the neck of the little boy, eight years of age, by Dr. DAVID W. CHEEVER, was communicated by him to the Boston Society for Medical Improvement, April 13, 1863; and published in the "Boston Medical and Surgical Journal," April 30, 1863: —

"This tumor, which was about as large as two closed fists, had existed for twelve months, but had increased very rapidly in size in the last month. As it showed no signs of softening, but was steadily enlarging, and had begun to create dyspnœa by pressure on the nerves and trachea, it was deemed best to attempt its removal. The skin moved freely over it. A number of enlarged cutaneous veins ran over it in various directions. The tumor felt to the touch lobulated and movable, as if made up of an enlarged chain of lymphatic glands. It extended from near the middle line of the neck in front, back upon the edge of the trapezius on the left side, and above, from the lobe of the ear and angle and body of the lower jaw, down to and beneath the clavicle. The left shoulder was depressed by it. The boy looked otherwise pretty healthy.

"March 31. — He was etherized; and an incision made from just below the ear to near the cricoid cartilage, through the skin and platysma, disclosed a lobulated, hard, glandular mass, lying mainly beneath, and partly behind, the sterno-mastoid muscle. Contrary to expectation, it was found very adherent in all directions, and the lobules bound together by strong, fibrous tissue. Considerable time and care were requisite to divide the adhesions, which were too strong to yield to any thing but the edge of the knife. It was found necessary to divide the sterno-mastoid, and dissect aside the external jugular which ran, somewhat displaced, over and through the tumor. The lower edge of the tumor extended beneath the clavicle, into and below the subclavian triangle. The base lay over the sheath of the carotid, which was necessarily exposed about two inches. Continuous dissection was required even to the last adhesion; for they could nowhere be made to yield at all."

The boy recovered in a few weeks, a large part of the wound healing by first intention. It is now eight months since the operation was performed, and there is no appearance of a return of the tumor. The boy is still somewhat pale, and a microscopic examination of his blood gives a larger number of white corpuscles than is usual in the normal condition. Within a few days, a similar case has presented itself in a boy seven years old, the same side of

the neck being affected. The enlargement of the glands in this case commenced about five months ago; and there is a large, lobulated, movable mass of them extending from just below and behind the ear to the clavicle in front, and also somewhat backwards upon the neck. They are soft, elastic, not painful to the touch or otherwise. The boy seems to be in good health, and the blood is not yet perceptibly affected.

Dr. Cheever has also met with a similar case since his removal of the tumor in the first one. These numerical hypertrophies of the lymphatic glands are of slow growth, and it is many months before the system becomes perceptibly affected by the introduction of their elements into the circulation. The consequences of the local suppuration of large masses of these glands are much more to be dreaded than the immediate effects of the introduction of an excessive number of their cellular elements into the blood, or even of a surgical operation. The latter may co-exist with the red blood-corpuscles for a long time without any serious results. Nor should an operation be discouraged whenever it is practicable, since, by this means, life may be prolonged, and the chances of recovery afforded.

In regard to the author's case of splenic leucocythemia, much might be said, as its whole history is the most remarkable of any in the records of this disease. The boy died April 17, 1863, exhausted by the diarrhœa which never wholly left him. No post-mortem examination could be obtained; but the enlarged liver and spleen could be distinctly felt through the abdominal walls, extending low down into the abdominal cavity. Two days before the boy's death, some blood was taken from his finger, which presented, upon microscopic examination an hour or two afterwards, numerous large, nearly colorless, or but faintly yellow crystals, having very distinct outlines. They

consisted, as regards form, of hexagonal and pentagonal plates of unequal sides, of rectangular plates in the form of squares and parallelograms, and also of a few triangular plates. Some of these crystals were twice the size of the red blood-corpuscles in the same field of view. They differed entirely, in form, size, color, degree of resistance to atmospheric influences, refractive and other properties, from all known crystals of the human blood. They were not at all permanent when exposed to the atmosphere, and disappeared in a few days. The author, in communicating his discovery of these crystals to the Suffolk District Medical Society, April 25, 1863, gave them the name of *Leucocrystallin*.

The photographs which accompany this Essay were taken from nature by Mr. William Hussey, of this city; and are exceedingly beautiful and valuable portraits of disease. The figures of the blood-corpuscles were also photographed by him from the original drawings.

In closing these prefatory remarks, the author is fully aware that a vast amount yet remains to be done in this new field of pathological investigation.

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ILLUSTRATIONS.

LEUCOCYTHEMIA.

Scarcely twenty years have elapsed since Professor Bennett of Edinburgh first announced to the medical world the discovery of a new disease, which he called "Leucocythemia, or white cell-blood." This new and comparatively rare disease has been the subject of much interest and inquiry ever since. But little additional light has been thrown upon its nature and symptoms, so fully were they delineated then. The most marked and fundamental characteristics of this disease are an augmentation of the white blood-globules and an hypertrophy of the spleen, not attributable to any anterior affection. A cachectic state, and a tendency to hemorrhages and diarrhœa, constitute some of its most frequent accompaniments.

In the year 1852, Professor Bennett published a work containing thirty-seven cases, more or less illustrative of the symptoms, pathology, and treatment of this disease. Since the appearance of his work, seve-

ral other cases of this disease have been reported in the various British, French, German, and other periodicals.

At the suggestion of Dr. Bennett, analyses were made of the blood of several of these patients, which show a remarkable uniformity in their results. These analyses have been confirmed by able chemists and microscopists; and the whole subject has passed through so searching an ordeal, that little is wanting to give it the character and precision of the facts and phenomena of positive science. A systematic account of this disease was prepared by M. Vidal, and published in a number of the *Gazette Hebdomadaire de Médecine*, April 4, 1856. This account, although carefully prepared, is considered by Bennett to be based upon too small a number of cases for any extensive generalizations.

The discovery of this disease has led to a more careful study of every thing which relates to the blood and the blood-making organs. Many of the observations of the older writers upon the blood acquire a significant importance by this accession to our knowledge. The office of the lymphatics, as demonstrated by Hewson nearly a century ago, receives additional confirmation from this source. His numerous papers and

experimental inquiries were the admiration of his contemporaries, and continue to be, in many respects, one of the most reliable sources of our knowledge upon those subjects even at the present day.

In the elaborate article upon the blood, in Simon's "Chemistry of Man," the opinions of Hewson stand side by side, in point of accuracy, with those of the most recent observers.

The literature of this subject is very voluminous; yet, in every modern work upon the blood or lymphatic system, we are sure, above all others, to find the name of Hewson. As his observations are to play so important a part in the consideration of our subject, let us make a rapid review of his works upon the lymphatics and the blood, before inquiring into the nature and causes of leucocythemia.

In reviewing the writings of Hewson, it would be unjust to pass over in silence those of his predecessors and contemporaries; for it is by comparing the efforts of both that we can justly appreciate the value of either. By this very process, we shall arrive at a more definite idea of the office of the lymphatics, and their connection with the blood, and thus be the better prepared to study the intimate nature of leucocythemia.

THE BLOOD.

HEWSON.

The first of Hewson's papers on the "Lymphatic System in Birds, Amphibia, and Fishes," was read before the Royal Society on the 8th of December, 1768. In a paper read before the same society on the 19th of January, 1769, Dr. Monro claims the discovery of the vessels which correspond, in the lower vertebrate animals, to the lacteals of the mammalia. A long and somewhat exciting controversy upon the priority of the discovery followed, although this honor did not strictly belong to either; since, more than a century previous, Thomas Bartholin had observed the lacteals in fishes, but erroneously supposed that they terminated in the liver. But, whoever was the original discoverer, it is certain that Hewson did more to explain and illustrate the lymphatic system in animals and man than any one of his predecessors and contemporaries.

When his last two papers on the lymphatic system of amphibia and fishes were communicated to the Royal Society by Dr. William Hunter, on the 16th of November, 1769, the following notice of them was placed upon record: "Mr. Hewson's descriptions

were greatly illustrated by the exhibition of a series of preparations taken from turtles and divers fishes, wherein these vessels were injected, and shown to the naked eye in their rise, progress, communications, and insertions, to the great satisfaction of the society. Thanks were returned to Dr. Hunter and Mr. Hewson for these very ingenious communications."

At a meeting of the Royal Society on the 22d of November, 1770, Sir Godfrey Copley's gold medal was awarded by ballot to Hewson "for his papers on the lymphatic system in birds, amphibious animals, and fishes."

His three papers on the properties of the blood were published in the "Philosophical Transactions" for 1770; and that on the "Figure and Composition of the Red Particles of the Blood, commonly called the Red Globules," in 1773. This paper was followed by another, upon the "Red Particles of the Blood, the Lymphatic Glands, the Thymus, and the Spleen." To these papers we are indebted for many of our most valuable ideas upon the blood and the blood-making organs.

Before the time of Hewson, the attention of observers was mainly directed to the coagulation of the blood. Many different opinions were held by the

older writers concerning this singular phenomenon. Aristotle thought it was owing to the presence of a fibrous matter, having noticed that it did not coagulate when the fibres were removed.

Harvey supposed, that, after death, the blood separated into two parts, — one dense and fibrous, the other ichorous and serous; the fibres connecting the whole.

Sydenham thought the buffy coat was solid and fibrous, and that the fibres were formed of the red part divested of its coloring matter. Thus, it is evident, he distinguished the blood-globules from the fibrine.

Boerhaave looked upon the fibrous portion of the blood as being chains of blood-globules; and Haller entertained a similar idea.

Leeuwenhoek, whose authority as a microscopist and whose speculative ideas had for so many years supplied the place of rigid experiments and careful deductions, appears to have regarded the blood as composed of globules and serum only; the globules alone being spontaneously coagulable.

About half a century after him, in 1735, Petit maintained, as a well-known phenomenon, that all the parts of the blood are not equally coagulable; that it

coagulates at first entirely; but, after a while, the serum separates from the clot "as whey does from curdled milk." From this he concluded that the lymph only coagulates, while the blood-globules and serum remain fluid.

Gaubius, in 1758, had a partial knowledge of the three proximate constituents of the blood, — the fibrine, the globules, and the serum.

Dr. Richard Davies, in 1760, had observed that the inflammatory pellicle was a kind of coagulated gluten, as he called it, belonging to the blood; and that the red globules possess no strong cohesion for each other, without the interposition of this substance. The same opinion was held by Dr. William Hunter concerning the coagulable principle. Very little else was then known of the blood besides its coagulability, and its separation into its proximate principles, — the fibrine, the globules, and the serum. The origin, growth, and destination of its corpuscular elements were still shrouded in mystery.

A wide field was open for discovery; yet many a writer was content to advance a theory, who lacked sufficient perseverance to search after the truth. Upon this field of labor, Hewson entered with a genius for observation and study hardly known in that

age. The result is shown in the works which he has left behind him, and which constitute one of the brightest pages in physiological discoveries. Whatever changes time may have wrought in our ideas upon these subjects, still the essential facts which he enunciated remain the same; and his theories of the origin and formation of the corpuscular elements of the blood are still received with only slight modifications.

He was almost the first to observe, that the shape of the blood-globules is not spherical, as their name indicates, but differs in different classes of animals, and, when out of the body, under different circumstances; the addition of water, for instance, converting them into spheres. He speaks of the general occurrence of these globules throughout the animal kingdom, and of the various colors which they assume in the insect tribes. Later observers have shown, that the color of insect blood is due, not to the corpuscles only, but to the *liquor sanguinis;* since the color is still preserved in absence of the corpuscles. Thus, in the greater part of the invertebrates, the blood is white, but red in the annelids, or worms; colorless in most of the mollusks; milk-white in many of the snails; but, in the *Helix Pomatia*, sky-blue; and, in the *Planorbis*

corneus, of a dark amethyst. The blood of the orthopterous insects is green; of the silk-worm, yellow; and of the coleopterous insects, or beetle tribe, dark brown.

More is now known concerning the shape of the blood-corpuscles, and the changes which they undergo during their development. In the oviparous vertebrates, they are at first minute, rounded molecules, which become elliptical cells, in which a nucleus and nucleoli are formed. These perfected corpuscles are regarded as analogous to the white ones in the viviparous vertebrates. Like them, when mature, their envelope probably dissolves slowly, forming a portion of the plastic matter of the blood; while the nuclei are set free, and, in the viviparous vertebrates, at length become the red corpuscles. Thus do the white corpuscles perform a duty somewhat similar to that of glands, in furnishing some of the plastic materials of the blood. Indeed, they have been called "the floating glands of the blood."

Wharton Jones speaks of three phases in the development of the blood-corpuscle; namely, that of the granule-cell, the nucleated cell, and the free cellæform nucleus. It is found in all of these phases in the blood of man and the mammals only. In the

lymph also of man and of the mammalia are found the granule-cell, the nucleated cell, and the free cellæform nucleus; but, in the lymph of the oviparous vertebrata, only granule-cells and nucleated cells are found. Thus a perfect correspondence is shown between the corpuscles of the blood and the lymph in these two great classes of the animal kingdom. This is, indeed, an important fact; and it will be much more clearly demonstrated, when we consider the office of the lymphatic glands in the formation of the blood-corpuscles.

The earlier microscopists found great difficulty in seeing the blood-corpuscles, so thickly were they crowded together. Hewson remedied this by diluting the blood with serum. He employed, in his examinations, single lenses of extremely short focal length. He gives plates of the blood-corpuscles of different animals, as seen with one of one-twenty-third of an inch in focal length, and consequently not magnifying more than one hundred and fifty diameters. Still, with such a lens as this, much and important work could be done by a good observer. Hewson discovered that the size of the blood-corpuscles does not depend upon the size of the animal in which they are found: thus those of the elephant and whale are

very much smaller than those of some reptiles. He found that saturated solutions of the neutral salts contracted the vesicular substance closely around the nucleus, and that the fixed vegetable and volatile alkalies corrugated the vesicles. From this he concluded, that Nature has set certain limits to the proportion between the water and salts of the blood, and that the latter are destined to preserve the peculiar disk-like form of the corpuscles. But this, we would rather suppose, is a vital phenomenon, from its constant occurrence and typical variations in the different classes of the animal kingdom, and not the direct result of chemical or physical forces. Thus Paget distinguishes vital force from all others by its power of generating typical organic forms.

THE BLOOD-MAKING ORGANS.

THE LYMPHATIC GLANDS.

Little is known to us of these glands during health; and it is only in disease that they are rendered perceptible in the living body. They are of a pale rose-color, excepting those of the lungs and the bronchial glands, in which a black pigment is found deposited in

the adult. They are larger in infancy and childhood than in mature life or old age, and in the male than in the female. They are subject to acute and chronic enlargements, accompanied by a cachectic and anæmic state of the system. So common is anæmia in these enlargements, that the chalybeates are almost always indicated. It is evident, then, that these glands are in some way connected with the blood-making system, and perform for it an important office. The security also of their general position, and the destination of their fluid and corpuscular contents to the thoracic duct and left subclavian vein, where they enter into direct communication with the lesser or pulmonary circulation, are in favor of this view. After passing through the lungs, the altered contents of the thoracic duct become mingled with the general circulation, and form a portion of the reconstructive material of the system.

Thus far, we have spoken of the lymphatic system only in the most general terms. There are several important organs of the body whose functions have been but very imperfectly known by physiologists, but which belong, without doubt, to this system.

The thymus and thyroid glands and the spleen, with other lesser bodies, are now classed with the lym-

phatics, under the general name of "blood-making glands." We need no higher authority than that of Hewson, Simon, and Sir Astley Cooper, to vindicate their claims to this position. It is futile to suppose, that organs of this size were made for no purpose, or are useless, as has been asserted of the spleen, because it can be excised in many animals without producing any obvious injury to their health. The thymus also, which assumes such wonderful proportions during fœtal existence and the first years of infancy, has been considered by some as the mere packing material of the anterior mediastinum. Nothing could be more absurd than to suppose that the Creator should resort to so unusual an expedient as this for so simple a purpose. Would it not be far wiser to suppose, that this organ, with its bountiful supply of nerves and blood-vessels, in close connection with the great aerating and circulatory systems of the body, should perform some more important office than the one assigned it?

We will consider, for the purpose of simplicity, each of the glandular organs separately; the office which it most probably performs in the blood-making processes, and afterwards its connection with leucocythemia.

THYMUS GLAND.

Sir Astley Cooper, in his beautiful monograph upon the thymus gland, describes it as composed of a cervical and a thoracic portion; the latter situated in the anterior mediastinum, the former extending upon the sides of the neck. It is just perceptible between the second and third months of fœtal life. It grows very rapidly from the seventh month until the time of birth; and even then continues to increase, or remain of the same size, during the first year. After this, it diminishes gradually until the time of puberty, when it usually disappears.

Haller says, "In the fœtus, it is an immense gland, and, together with the pancreas and thyroid, is the greatest of the glands, — hardly less than the kidney."

Meckel says, "Notwithstanding its proportional volume is not so considerable at the end of the first year, and sometimes even at that of the second, it continues to increase during all this period. It becomes effaced, in an inverse sense, to that in which it was formed; that is to say, from below upwards. No trace is ordinarily found of it at the twelfth year; and the place which it occupied is then filled with fat."

Hewson describes this gland as continuing to grow to the end of the first year after birth; remaining

nearly stationary during the next two years, and then decreasing until about the twelfth year, at which time it usually disappears. He never saw it, he says, at puberty.

Cloquet's description is very similar to that of Meckel. Later observers have seen the thymus in adult life.

The fluid from the thymus, according to Hewson, is the same as that found in the lymphatic glands. It consists of a "great number of small white, solid particles, exactly resembling, in size and shape, the central particles in the vesicles of the blood, or such as are found in the fluid of the lymphatic glands. As to the excretory duct of the thymus, it was shown by him to consist of the lymphatic vessels connected with it, and ramifying throughout its substance. Large quantities of the white particles being found in these vessels, first led him to suspect that they were the excretory duct. This fact he afterwards demonstrated by several careful and conclusive experiments.

In speaking of the physiology of this gland, Cooper says, "Hewson was of opinion, that the thymus gland formed the internal part of the red globules of the blood, and that the red particles were composed of two portions; viz., a small central particle pro-

duced by the thymus, and a vesicular part formed by the spleen." He quotes the following account of the use of the thymus from Hewson: —

"The thymus gland, then, we consider an appendage to the lymphatic glands, for the more perfectly and expeditiously forming the central particles of the blood in the fœtus and in the early part of life. The structure and uses of this gland are similar to those of the lymphatic glands, to which it may be considered an appendage."

In commenting upon the foregoing passages, Sir Astley Cooper says, "It is quite at variance with my feelings to find fault with Hewson, who was an excellent anatomist and a highly ingenious man, and for whose memory I have the highest possible respect; but I cannot agree with the opinion, that the structure of the thymus and absorbent glands is similar: one is conglobate, and the other conglomerate; one is firm and compact, and the other is loose and pulpy; the one contains cells of considerable magnitude when in a distended state, whilst in the absorbent glands the cavities are small, and with so much difficulty traced, that there is still a doubt if they be cellular or vascular." Since the above was written, the nice distinctions drawn by Cooper between these glands are no

longer adhered to as of any essential importance. The name of *vascular glands* has been given to all of these glandular organs destitute of a proper excretory duct.

Sir Astley Cooper concludes his chapter upon the physiology of the thymus with the following query: "As the thymus secretes all the parts of the blood, — viz., albumen, fibrine, and particles, — is it not probable that the gland is designed to prepare a fluid well fitted for the fœtal growth and nourishment from the blood of the mother before the birth of the fœtus, and consequently before chyle is formed from food? And this process continues for a short time after birth, the quantity of fluid secreted from the thymus gradually declining as that of chylification becomes perfectly established."

It is evident from the foregoing query, as well as from other portions of his essay, that Sir Astley Cooper indorses, on the whole, the opinions of Hewson, even if he does not his precise language.

The rapid progress of comparative anatomy and physiology tends to give us more correct ideas of the functions which different organs perform in the animal economy. Shape and size alone cannot determine definitely, beforehand, the office of any organ or part. Disease or some well-directed experiment may en-

lighten us upon its functions, which might otherwise be obscure; but who shall say, from mere examination, why the liver should secrete the bile, the kidneys the urine, the salivary glands the saliva, or the spleen, thymus, and lymphatic glands, the nuclei and corpuscles of the blood?

Cooper mentions only one case of disease of the thymus. This occurred in a girl seventeen years old, and was accompanied by bronchocele, or enlarged thyroid. Death took place from pressure upon the trachea. The disease is described as of a "fungoid" nature and yellowish-white color. Nothing is said about its microscopical appearance; and it was probably not examined.

Wedl mentions premature atrophy of the thymus as occurring particularly in children affected with marasmus. Its entire absence has been observed only in cases of acephalism. Inflammation of this body is rare. Hasse mentions two cases, in one of which an abscess opened into the trachea. In tuberculosis, the thymus occasionally becomes affected: it sometimes, also, suffers from hypertrophy.

Thus, from the ordinary diseases of this organ, it would be very difficult to determine its functions. Its embryology throws more light upon the subject.

THYROID GLAND.

Happily, our knowledge of the thyroid is of a much more positive nature. The most common disease of this gland is hypertrophy, or bronchocele. Erichsen speaks of this disease in the following manner: "There is a remarkable connection between tumors of the thyroid gland of this kind and a general anæmic condition of the system. In London, nothing is more common than to find a certain degree of bronchocele in pale and bloodless women and girls. Indeed, so frequent is the coincidence, that it is impossible not to regard it in the light of cause and effect."

Hasse speaks of simple enlargement of the thyroid as frequent. Handfield Jones says, "The affection is almost wholly confined to youth, and is frequent about the age of puberty in both sexes; more so, however, in the female, in whom enlargement is especially apt to prevail at the approach of the menstrual period."

All we can learn from the above authorities is, that the enlargement of the thyroid is generally associated with some change or derangement of the blood. Bennett has recorded a case of diseased thyroid, in which microscopical examinations were made of the contents

of this gland, and also of the blood of the patient. In this case, which was that of a female who died at sixty with cancer of the lung, the thyroid body and lymphatic glands of the neck were involved, and the blood was *leucocythemic*. Besides the cancer-cells found in these organs, were a considerable number of round, colorless corpuscles, varying in diameter from the hundred and fiftieth to the hundredth of a millimetre. An unusual number of these cells also existed in the blood, as was determined both before and after death. The most remarkable feature of the case was this: "The cells and included nuclei of the thyroid body were considerably smaller than usual; and it was ascertained that the colorless bodies in the blood, and their nuclei, were smaller also." Thus, he continues, "*it was seen, that the colorless corpuscles in the blood were of two distinct sizes, — the smaller corresponding with the nuclei of the larger ones; and the lymphatic glands were found to be crowded with corpuscles, also of two distinct sizes, exactly corresponding to those in the blood.*" What better evidence could we have, that the colorless corpuscles are formed in these appendages to the lymphatic system, from which they readily find their way into the blood? The fact of the smaller corpuscles exactly correspond-

ing in size with the nuclei of the larger ones cannot be merely accidental. This increase in the number of the white corpuscles in the blood, has, in every known instance, been preceded by hypertrophy of some of the lymphatic glandular organs, more especially the spleen. Thus it is shown most conclusively, that it is the diseased glands which give rise to an excess in the number of white corpuscles in the blood.

THE SPLEEN.

In health, the spleen ordinarily weighs from six to ten ounces, and is situated on the left side, between the eighth and tenth ribs, and next to the diaphragm. Soon after death, it resembles the blood in color, but gradually becomes of a dark, leaden hue. It may, with propriety, be regarded as a mere congeries of arteries, veins, nerves, and lymphatic vessels. It has no proper excretory duct; but this office is fulfilled by the lymphatic vessels and veins with which this organ is so amply supplied. Hewson found the lymphatic vessels so numerous in the spleen of fishes, that the gland was equally well colored by injecting them as by injecting the arteries.

The secreting cells of the spleen are covered by a network of veins and arteries which ramify over their

surfaces. Into the veins and lymphatic vessels its proper secretions are carried, after they have been elaborated by the gland from the arterial blood, and thus find their way into the portal circulation. Here the white corpuscles are found most abundant; but, after the blood has passed through the pulmonary circulation, it is not usual to find, except in cases of leucocythemia, more than one white to three hundred and fifty red blood-corpuscles. The production of plasmic, or colorless blood-corpuscles, is very active in the spleen; and the extirpation of this organ is followed by a diminution in their number, although it is most probable that its function, in this case, is supplied, in a measure, by the increased activity of the other blood-making organs. Funke has noticed the great abundance of these corpuscles in the healthy spleen; as has also Virchow. Gray has observed the same phenomenon, and considers them identical with those that are ordinarily found in the blood, and insists on their perfect resemblance to the constituent cells of the spleen. Vierordt has found the white corpuscles in the splenic blood to be from one-fourth to one-ninth as numerous as the red ones. Hirt gives the relative number of red globules to one white one in the arterial and venous blood of this organ, as follows: —

	Arterial Blood.	Venous Blood.
1st observation	2600	74
2d „	1843	54
3d „	2095	82

Thus, for the same number of red globules, there was over thirty times as many white ones in the blood which left the spleen as in that which arrived at this organ. Gray has observed, that the blood generally contains less solid matter after its passage through the spleen than before entering it, and that this impoverishment is confined to the diminution of the number of its red globules. In horses badly nourished, or deprived of food, this diminution in the relative number of the red blood-globules in the spleen became less apparent. Führer has noticed the rapid destruction of blood-globules in the spleen in its enlargements after intermittent fever.

What interpretations shall we give to these statements? Do they not show an astonishing diminution of the red corpuscles in their passage through the spleen, and, at the same time, the formation of the white ones there in greater abundance than elsewhere; or, in other words, both a destructive and a reconstructive metamorphosis in the same organ? But do we not have something quite analogous to this in the liver? Does not this organ secrete sugar and excrete

bile, and with it a portion of the coloring matter of the blood, as well as assist in the elimination of different substances introduced into the system? If the red globules of the blood are destroyed in the spleen, as has been asserted of them, then will their destruction be the more rapid, the more numerous the constituent elements or cells of that organ become; and, finally, in place of the ntricles or perfectly developed blood-cells, we shall have only the nucleated or immature plasmic cells, or, in other words, the white blood-corpuscles. All of these conditions are found in leucocythemia.

THE LIVER.

ORIGIN OF THE BLOOD-CORPUSCLES.

Those micrographers who have studied most profoundly the origin of the blood-globules in batrachians and fishes have nearly all agreed, that the primitive blood-cells bear a close resemblance to the cells of the surrounding tissues. Many, indeed, have gone so far as to declare them identical. Among those who have done most to establish this idea are Baumgärtner and Schultz, who suppose these primordial globules to be spherules from the vitellus; the latter supposing them

to become surrounded by an utricular membrane, — an opinion which has been combated by Valentin. Reichert has also endeavored to show, in the tadpole and chick, the close analogy between the blood-cells and tissue-cells of the embryo. Vogt believes that the origin of the blood-corpuscles is in the blastodermic layer, which reposes directly upon the vitellus, and which is designated by him under the name of *hæmatogenic* layer. The formation of the coloring matter of these corpuscles — which is regarded by chemists as an animal dye — is the result of a physiological process which is closely allied to, if not identical with, secretion. Thus each one of these corpuscles is a living organ or organite, endowed with important and peculiar functions, and furnishing to the economy its elaborated products. In their earliest stages, in oviparous vertebrates, their included nuclei undergo fissiparous multiplication; the diaphanous cell-wall becoming constricted as the nucleus becomes divided, so as to form new enclosures for the separated nuclei.

Hugo Von Mohl and Braun have shown a similar mode of cell-division in the vegetable kingdom. The above observations are also equally applicable to the formation of the blood-corpuscles in the embryos of viviparous vertebrates and man.

After the formation of the liver, the multiplication of the blood-globules by fissiparation ceases. From this fact, Prevost and Dumas have drawn the inference, that the typical blood-globules have their seat of formation in this organ.

Kölliker has seen all the stages of transformation between the colorless and colored corpuscle in the blood of the liver in the embryos of the mammalia; and he is of opinion, that, at a certain period of fœtal life, the blood-globules are formed solely in this organ. He is probably, in a great measure, correct; but it cannot be denied, that other organs at the same time share extensively in the formation of these elements of the blood. Weber is of opinion, that these globules arise out of the epithelial cells of the delicate walls of the capillaries of the liver. Remak thinks that they are not derived from the constituent cells of the liver; as they could not enter the circulation, on account of the limitary membrane of the hepatic vessels. Later observations tend to show that the colored are derived from the colorless corpuscles, and that their formation in the human blood is due to a large number of glandular organs.

LEUCOCYTHEMIA.

BENNETT.

Having spoken of the blood and the blood-making organs in a somewhat general manner in relation to this subject, let us now consider leucocythemia in a clinical, microscopical, and physiological point of view. It will be necessary, for the purpose of simplicity, to review the principal writers upon this subject separately, and in the chronological order of their publications, as nearly as it can be ascertained. In this manner, much discussion as to the priority of discovery will be avoided.

As regards the clinical history of leucocythemia, a few cases from Bennett are sufficient to characterize this as a newly-discovered disease. It has probably been confounded by previous writers with pyæmia, or pus in the blood. As there is no ready way of distinguishing blood containing pus from white cell-blood, it is easy to see how this mistake could have often been made. But the history of pyæmia, which is always connected with some local inflammation and suppuration by which pus is introduced into the blood, is sufficient to distinguish it from leucocythemia, which comes on in a very gradual and insidious manner,

accompanied by altogether different symptoms, and invariably preceded by chronic enlargement of some of the lymphatic or blood-making glands.

Case I. — The first case of leucocythemia was published by Professor Bennett in the Edinburgh Journal for the 1st of October, 1845. The subject of it was John Monteith, a slater, aged twenty-eight years; complexion dark; usually healthy and temperate; admitted into the Royal Infirmary, Feb. 27, 1845. The following is a condensed history of the case: For the last twenty months, a tumor appeared in left side of abdomen, which has gradually increased in size until within four months, — not painful. Other tumors have since appeared in neck, axillæ, and groins; at first, painful. Previous to June last, vomited frequently in the morning; usually constipated; appetite and digestion good. On admission, the tumor extends from ribs to groin, and spinal column to umbilicus, on left side. Dull on percussion, and painful near upper part on pressure. Pulse 90; slight œdema of legs; urine turbid, natural in color; acid to litmus, sp. gr. 1013, unaffected by nitric acid. March 9, œdema of legs has increased. March 10, tormina and diarrhœa. March 13, thirsty; skin hot; pulse 110; diarrhœa

checked by opium; urine, a hundred ounces. March 14, diarrhœa continues; pulse 100; tongue dry and brown; countenance of typhus. March 15, died suddenly, in the morning.

Sectio Cadaveris.

Prominence of tumor well marked externally. Ascites and œdema of limbs gone. Blood throughout the body separated into a yellow and brick-red portion. Blood-vessels, substance of brain, and lungs, healthy. Heart somewhat enlarged; weighed eleven and a half ounces; texture healthy; valves normal. Firm coagula in right auricle, ventricle, and pulmonary artery. Liver enormously hypertrophied; structure healthy. Gall-bladder enlarged; contents, pale yellow; weight of both, ten pounds and twelve ounces. Spleen also greatly enlarged, fusiform; weight, seven pounds and twelve ounces; length, fourteen inches; breadth, seven inches; and thickness, four and a half inches. Kidneys healthy. Lymphatic glands everywhere much enlarged. Several of the inguinal glands the size of a walnut, and even larger. So also of the axillary glands. Bronchial glands enlarged; dark purple and black in places, from pigmentary deposit. The mesenteric and lumbar glands also much enlarged. No pus found in any of the tissues.

Microscopic Examination.

Numerous colorless corpuscles were found in the yellow coagula. These varied in size, from the eightieth to the hundred and twentieth of a millimetre in diameter. Acetic acid showed a distinct nucleus in some, about the two hundredth of a millimetre in diameter; in others it was divided into three smaller ones. White corpuscles and granules were found in the different lymphatic glands.

In relation to this case, Professor Bennett says, "*There was no phlebitis, abscess, or purulent collection, to which the appearances within the vessels could be ascribed.*" He thinks the only bodies which they resemble are the colorless blood-corpuscles, but that no instance was known in which they were found in such numbers; that they originated in the blood system itself, as M. Bouchut has shown in various chronic diseases.

About six weeks after this, Professor Virchow, of Berlin, published a similar case, in which he confirmed the opinion of Bennett, that these were the colorless corpuscles of the blood. Thus was he enabled, from his previous pathological studies, to confirm what Bennett had already surmised. The discovery, then, of leucocythemia belongs almost

equally to both writers. Nor are these singular coincidences uncommon in the history of medical discoveries. Thus were the discoveries of Schwann, in regard to the origin and development of the animal cell, made almost simultaneously with those of Schleiden in relation to the vegetable cell.

Case II. — Let us give, in a condensed form, two more characteristic cases from Bennett. Barney Finley, aged seventeen, farm-servant. Admitted into the Royal Infirmary, Jan. 25, 1850. About three years ago, had scarlet fever. With this exception, has had perfect health until one year ago. Then noticed a tumor in abdomen somewhat painful, which has since increased in size so as to cause dyspnœa in walking. On admission, pale and cachectic. A hard tumor can be felt occupying the whole left side, from the false ribs to within an inch and a half of the symphysis pubis, and extending backwards to within three inches of the spinous processes of the lumbar vertebræ. Liver, on percussion, found natural; tongue clean; appetite good. Has had profuse diarrhœa for the last three or four weeks. Pulse 80; weak; some vertigo; sounds of heart natural. Has occasional epistaxis, and hemorrhage from the gums. Respiratory and

urinary systems healthy. Blood drawn from finger contained the colorless corpuscles in great numbers. Acetic acid brought into view a single nucleus in some; but, in the majority, two, three, and even four nuclei with depressed centres. Occasionally the nucleus was crescentic.

Jan. 27, diarrhœa diminished; less pain.

Examination of Blood.

Specific gravity of the blood	1041.5
Specific gravity of the serum	1026.5

Composition of 1000 *Parts.*

Fibrine	6.0
Serous solids	72.0
Globules	67.5
Total solids	145.5
Water	854.5
	1000.0

Feb. 2, urine loaded with lithates; diarrhœa returned. March 24, during the last few weeks, recurrence of hemorrhage from nose and gums; ascites not abated. Aug. 7, more or less recurrence of diarrhœa and epistaxis during the last six months. Ascites not all gone. Dismissed, and returned home. Died July 22, 1851, extremely emaciated.

Post-mortem Examination and Report of Dr. Sandwith.

Heart very small; lungs healthy; liver weighed three pounds and twelve ounces; spleen weighed three pounds and fourteen ounces; mesenteric glands enlarged and pale; kidneys small, — weighed together six ounces. Microscopic examination of the blood showed numerous white corpuscles.

This case was remarkable for its duration, and the persistent recurrence of the diarrhœa under energetic treatment and most favorable hygienic circumstances. The spleen was the principal organ involved; but the lymphatic glands were also somewhat enlarged. Ascites was a marked feature of the case. There was no perceptible change in the number of white corpuscles in the blood while under treatment. During the progress of the disease, the fibrine increased to twice the amount usually found in healthy blood; the albumen and salts remained normal; the globules were diminished to one-half their usual number; the water was proportionally increased. Thus we have a condition of the blood peculiar to no other known disease; at least, to the same extent. We have a disease, too, which has thus far been singularly fatal; whose

diagnosis admits of very little doubt; and the prognosis of which, when well marked, is any thing but favorable. Is it not singular, then, that this disease should have so long escaped the attention of observers? It is to the microscope, as a means of diagnosis, that we owe its discovery. The relations between these different glandular enlargements and the multiplication of the white corpuscles in the blood would never have been known without it.

In the two instances of leucocythemia already quoted, the spleen, liver, and lymphatic glands, were all hypertrophied in one; and the spleen and mesenteric glands, in the other. In the latter case, there was ascites, and the kidneys were somewhat atrophied. In the one which we are about to condense from the same author, the spleen and liver were both enlarged, and the patient had ascites. The urine, in both cases where ascites existed, was loaded with the lithates.

Case III. — Thomas Welsh, sailor, aged twenty. Admitted into the Royal Infirmary, Sept. 22, 1851. In June, 1847, first experienced pain and swelling in splenic region; shortly afterwards, had swelling also in right side of abdomen, followed by jaundice. The latter disappeared, and he regained his health. Had

occasional attacks of jaundice since, and abdomen has slowly enlarged.

On admission, is generally emaciated; abdomen enlarged; no ascites. Extensive hepatic and splenic dulness. Bowels loose; respiration embarrassed; impulse of heart feeble; pulse 78. Of small stature and sallow skin. Urine healthy. The relative number of colorless and colored corpuscles, thus far, unchanged. Had occasional diarrhœa and epistaxis until October. During this month, had a severe attack of laryngitis. In the latter part of December, ascites came on: the urine was diminished in quantity, and loaded with lithates. The blood was examined from time to time; and, on the 3d of January, a decided increase of the colorless corpuscles was observed. The ascites was diminished by diuretics: but the colorless corpuscles continued to increase; considerable groups of these bodies being seen between the rolls of colored disks under the microscope. His strength became much diminished; but he left the infirmary, Feb. 27, 1852. He died two days after reaching Berwick.

There was no *post-mortem* examination. The following analysis of his blood was made by Dr. W. Robertson on the 7th of January: —

Density of blood	1043.5
Density of serum	1027.0

Composition of 1000 *Parts.*

Fibrine		3.2
Serous solids	organic, 70.4; inorganic, 10.3	80.7
Globules		82.3
Total solids		166.2
Water		833.8
		1000.0

In this instance, the disease was seen throughout its entire course; and the period at which the colorless corpuscles of the blood began to increase was also observed, as it has since been in other cases.

Nearly twenty other cases of leucocythemia are recorded by Bennett as coming under his notice since the publication of his work upon the subject in 1852. The details of eight or ten of these cases, and a table containing the characteristic features of the others, are given in his "Lectures on Clinical Medicine," published in 1860. To these is added a somewhat elaborate discussion of the subject from a physiological point of view.

	Name.	Age.	Degree.	Liver.	Spleen.	Abdominal Glands.	Remarks.
1	Tho. Christie	15	Advanced.				Not examined after death.
2	Wm. Baillie	43	Advanced.	*lbs.* *oz.* 3 10	*lbs.* *oz.* 2 4	Little enlarged.	
3	Pat. Flood	13	Well marked.				Dismissed from the house; did not return.
4	Jn. Gaffney	16	Moderate.	6 14	0 22	Twice natural size.	
5	Chas. Rennie	19	Well marked.	4 7	2 14	Enlarged.	
6	J. M'Arthur	25	Moderate.	3 5	0 6	Highly Tubercular.	Tubercular Peritonitis.
7	Eliz. Pollock	56	Advanced.				Not examined after death.
8	Wm. Dods	23	Slight.	3 2	0 5	Greatly enlarged.	Cancer in various organs.
9	T. Crease	28	Moderate.	2 8	0 6	Mucous coat of ileum thickened.	Cancer in Lung.
10	Eliz. Barker	17	Slight.	2 7	Natural.	Enlarged.	Tubercular Peritonitis.
11	Janet Young	50	Moderate.	2 0	Natural.	Not mentioned.	Aneurism. Waxy kidneys.
12	John Young	27	Well marked.	Natural.	14 oz. dense.	Not mentioned.	Cerebral Hemorrhage. Glanders?
13	G. Harper	60	Advanced.	Natural.	8 lbs., with deposit.	Little enlarged.	
14	Ber. Collins	35	Well marked.	5 10	0 27	Not enlarged.	Pneumonia. Tubercle in Lungs.
15	D. Cockfield	32	Slight.	6 8	22 oz. deposit.	Little enlarged.	Bright's Disease.
16	J. M'Gregor	32	Slight.	5 11	0 16	Much enlarged.	Melæna.
17	Jer. Brown	29	Advanced.	5 9	3 13	Enlarged.	Acute Tuberculosis.
18	John Short	50	Well marked.	4 0	8 oz. dense.	Not enlarged.	Bright's Disease.

Let us, then, examine the peculiar views of Bennett, before passing to the consideration of the labors of others. In this manner, we shall give more unity to our subject; since each author's cases must necessarily serve to illustrate his ideas of the disease. Let us examine, for a moment, his ideas of its pathology.

Among the hypertrophies, which are always more or less present, the spleen has most usually been affected. The enlargement in these cases was chiefly owing to numerical hypertrophy. Next in frequency, the liver has been found enlarged. In a few instances, it was found in a state of cirrhosis, or even cancerous. The lymphatic glands are also prone to be similarly affected. Hypertrophy of the thyroid gland, or bronchocele, has, in a few cases, given rise to leucocythemia. Bennett gives the details of a very interesting case of this kind. He also mentions others in which the blood was found in this condition by Drs. Holland and Neale.

Disease of the supra-renal glands is mentioned as sometimes associated with a leucocythemic condition of the blood. Considerable difference is found in the relative proportion between the white and red corpuscles in different cases. Sometimes they are

nearly equal in number; at others, the white ones exceed the red: but, in the majority of instances, the red ones are found in the largest numbers. Different fields of the microscope are found to present the two kinds of corpuscles in somewhat different relative proportions. Sometimes the white corpuscles will cluster more thickly along the borders of the streak of blood, and thus appear much more numerous than they otherwise would. It requires much time and care to approximate even to their relative numbers. The white corpuscles differ also considerably in size. They are from two to three times the diameter of the red ones. In two cases mentioned by Bennett, they were of the same size as the red corpuscles; in one of which, there was also the larger variety at the same time. They contained from one to four nuclei; or, in some cases, an elongated and crescentic nucleus. This is ultimately divided into two or more nuclei.

From an analysis of the blood in several of the foregoing cases, the fibrine was generally found to be increased, and the corpuscles diminished. The fibrine ranged between three and seven parts, and the corpuscles from one hundred to forty-nine parts in a thousand.

It is, according to Bennett, the opinion of many physiologists, that the colored corpuscles are formed directly from the colorless corpuscles of the blood. Others suppose, that, whilst this may be the case in fishes, reptiles, and birds, in mammals the colored corpuscle is the liberated nucleus of the colorless one.

This latter view accords with the observations of Bennett upon the blood-corpuscles in leucocythemia. The following is his idea of the process of transformation: The nucleus of the colorless cell becomes divided into two, three, and four nuclei; the cell-wall gradually dissolves, and the nuclei escape into the circulation, and become the colored corpuscles, whilst still in the nuclear stage of growth. Some of them, however, acquire cell-walls. "Under such circumstances," says Bennett, "the nuclei increase endogenously by a process of fissiparous division, in the manner formerly described; circulate in the blood within colorless cells; and, on the solution of the cell-wall, also become colored blood-disks."

Let us now, for a moment, apply this theory of cell-growth to the rational explanation of leucocythemia. In this disease, then, we have an excessive multiplication of the white corpuscles of the blood, and, at the

same time, a persistence of their cell-membrane, even after entering the systemic circulation; or, in other words, we have an excessive growth of imperfectly developed blood-cells. In such cases, the cell-membrane, or parent cell, still encloses its multiple nucleus. Sometimes these nuclei present a distinct depression, or shadowed spot in their centres; at others, the nucleus becomes oval, elongated, or even crescentic, containing, at the same time, two or three granules with depressed centres.

"On one occasion," says Bennett, "the colorless bodies in the blood were of two distinct sizes. The smaller were evidently free nuclei, such as could be observed within the larger."

The lymphatic glands in this case were observed to contain the smaller bodies in great numbers, associated with a few of the larger ones. Thus it would seem, that the white corpuscles of the blood are only lymph-corpuscles with the addition of a cell-membrane. If this position be acceded to, and certainly it is in harmony with the observations of the latest and best writers upon these subjects, what more can we desire for the rational explanation of the causes of leucocythemia? Is it not the tendency of modern investigations to trace all pathological back to physiological

processes? Do we not see in the enlarged glands, which are always met with in leucocythemia, a sufficient cause for the increased production of cell elements? Thus has the power of forming white blood-corpuscles been increased in proportion to the extent of this glandular hypertrophy. In those instances in which the progress of leucocythemia has been observed from the first appearance of any increase of the white corpuscles in the blood, the enlargement of the spleen or some other lymphatic glandular organ has always preceded this change. Thus the hypertrophy of the spleen and other lymphatic glandular organs must be considered as the cause, and not as the consequence, of leucocythemia.

The cause, then, of leucocythemia, is so intimately connected with the origin of the blood-corpuscles, that a thorough consideration of this disease necessarily involves an inquiry into the sources from which they are derived.

Whatever light may be thrown upon this obscure point by comparative physiology, Bennett has made use of to illustrate his theories. The origin and mode of development of the blood-corpuscle, as at present known, in fishes, reptiles, and birds, are carefully compared with the origin and development of those in

man. He concludes the subject of leucocythemia in the following brief paragraphs: —

1st, "The blood-corpuscles of vertebrate animals are originally formed in the lymphatic glandular system; and that the great majority of them, on joining the circulation, become colored in a manner that is as yet unexplained. Hence the blood-corpuscles may be considered as a secretion from the lymphatic glands; although, in the higher animals, that secretion only becomes fully formed after it has received color by exposure to oxygen in the lungs."

2d, "That, in mammalia, the lymphatic glandular system is composed of the spleen, thymus, thyroid, supra-renal, pituitary, pineal, and lymphatic glands."

3d, "That in fishes, reptiles, and birds, the colored blood-corpuscles are nucleated cells, originating in these glands: but that, in mammals, they are free nuclei, sometimes derived as such from the glands; at others, developed within colorless cells."

4th, "That, in certain hypertrophies of the lymphatic glands in man, their cell-elements are multiplied to an unusual extent, and under such circumstances find their way into the blood, and constitute an increase in the number of its colorless cells. A corresponding

diminution in the formation of free nuclei, and consequently of colored corpuscles, must also occur. This is leucocythemia."

In the London "Lancet" for Jan. 3, 1863, will be found the first of a course of lectures now being delivered by Professor Bennett, "On Molecular Physiology, Pathology, and Therapeutics." In these lectures, which are an exposition of his latest views upon cell-development, he advances the well-known theory of the agency of molecules in growth and disintegration. He characterizes these processes of formation and disintegration by the names of *histogenetic* and *histolytic* processes. He speaks of these molecules as being of three different kinds, — albuminous, fatty, and mineral compounds. He illustrates, by a figure from Rainey, the process by which mineral molecules coalesce into cell-forms. Several of these forms are shown, which bear a striking resemblance to what we observe in the growth of vegetable and mineral cells. Whether this is a mere casual resemblance or not, is a matter well worthy of the attention of physiologists.

In the "Lancet" of Jan. 17, 1863, is the second of Bennett's course of lectures. In this lecture he brings forward three prominent theories of cell-development, — that of Schleiden and Schwann (1839), of Goodsir

(1845), and of Huxley (1853). The first of these is known to every physiologist: the second does not essentially differ from the first. This theory regards the nucleus as the centre of nutrition and germination. The third theory, or that of Huxley, considers the nucleus as a comparatively unimportant element, and ascribes all morphological and chemical changes to the *periplast*, or cell-wall. This last theory is not strictly one of cell-genesis, but of the morphological growth of cells.

Bennett's theory in regard to the reproduction of cells is this: There are four different modes in which cells may arise: —

1st, Endogenously, or cell within cell.

2d, Exogenously, or outside of cells by extrusion of contents.

3d, Fissiparously, or by division.

4th, Gemmiferously, or by the process of budding.

These may all be seen in one plant, proceeding together.

The first and second modes are most common in adult animals; the third, in the embryo.

Previous to the publication of Huxley's views, the late Dr. Waldo I. Burnett, of Boston, made an elaborate study of cell-development in animals, and, to some

extent, in plants. In his admirable prize essay upon this subject, he shows very clearly, at least in animal cells, that the nucleus is a hollow vesicle, or utricle, which becomes enlarged by endosmosis; the contents of which may afterwards become condensed to form a nucleolus or another similar utricle.

A similar mode of cell-origin has been shown in plants by Braun and other physiologists.

Dr. Burnett regards the embryonic blood-cell of both the oviparous and mammalian vertebrates as "of an epithelial nature, and simply provisional." He thinks that adult blood, which is elaborated from the food alone, contains typical corpuscles. As regards the blood-corpuscles of the mammalia, he is of opinion that they "are formed around the granules which constitute the compound nucleus of the chyle-cell; the nucleus afterwards becoming dissolved, and, in nearly every instance, entirely passing away." This theory is confirmed, in a great measure, by the transition stages which have been found in many of the blood-corpuscles of leucocythemia.

In closing this review of Professor Bennett's labors, it is but just to say, that he has already done more than any one else, of late years, to excite a lively interest in the study of the pathology of the morpholo-

gical elements of the blood; and it is to be hoped, that his present course of lectures will not be without their good effect in this direction.

VIRCHOW.

From a careful comparison of the writings of Bennett and of Virchow upon leucocythemia, it is impossible to find any essential difference in the views of either as regards the origin or nature of this disease. Both are agreed, that numerical hypertrophy of the spleen, or multiplication of its cellular elements, is the principal cause of the increased number of white corpuscles in the blood. Both are equally agreed, that the same kind of hypertrophy of other lymphatic glands is also the cause of a leucocythemic condition of the blood.

Bennett makes no distinction between the different varieties of leucocythemia as regards its origin, but considers them all essentially the same. Virchow divides this disease into two distinct varieties, — the splenic and lymphatic, according to the organs affected. Both authors regard numerical hypertrophy of the spleen as the most common cause of this disease.

Let us now consider more fully the views entertained by Virchow upon this subject. These views are given

at some length and with great clearness in his recent work on "Cellular Pathology." So interwoven are they, however, with his cell-doctrines, that their unity and beauty are, in a measure, lost by being separated. Nevertheless, in the limited space which must be allotted to them in this essay, let us give an adequate idea, if possible, of these views.

That remarkable change by which the blood for a time contains more than its usual number of white corpuscles has been denominated by Virchow, *leucocytosis*. This temporary condition of the blood is not an unusual one. After every full meal, there exists, according to this author, what may be properly called a *physiological leucocytosis*, or augmentation of the white blood-corpuscles in the circulation. This phenomenon is attributed by him to the irritation of the mesenteric glands during digestion by the large quantities of material passing through them, and is considered a strictly normal one.

In disease, however, of these or any other of the lymphatic glands, provided that the disease has not proceeded so far as to interfere with their functions, there is also a more or less permanent leucocytosis, or increase of the white-blood corpuscles. To this more permanent condition of the blood, he has given the

name of "Leukæmia," or "white blood." It must be remarked, that, in the physiological leucocytosis, there is but a very inconsiderable and transitory increase in the number of white blood-corpuscles; while, in the permanent or pathological leucocytosis, their number is gradually augmented, until it almost equals, in some cases, that of the red blood-corpuscles.

As to the amount of this increase of the white corpuscles during digestion, Virchow has given us no approximate idea. Milne Edwards states, that, in a series of experiments upon the numerical relation between the red globules and the white, before and after meals, Donders and Moleschott found, that, in the rabbit, the proportion of the latter augments considerably during the process of digestion. Thus, upon counting the number of white globules which were found in the field of the microscope, arranged so as to contain about two thousand red globules, they have seen one or two of these globules (corpuscles) in the morning, when the animal had fasted during the night; a little while after he had eaten, the number increased to four, then to ten; three hours after the meal, it diminished again; and, after an interval of nine hours, fell to nearly the same rate as in the morning.

In man, the influence of meals was equally marked by an augmentation in the proportion of the white globules; but the difference was not so great.

In another series of analogous observations, Moleschott has also seen that the proportion of white globules is diminished by abstinence, and augmented by starchy food. Dr. E. Hirt has published a more extended work upon the same subject; and he has represented by curves the relative numbers of the red globules and of the plasmic or lymphatic cells observed in the blood during different periods of the digestive process. Indeed, under these circumstances, the absolute number of red globules does not seem to vary notably; and, consequently, the differences in the proportion of the white corpuscles can be considered as being the expression of the variations in their real number. In the morning, fasting, the proportion of these corpuscles was about one white globule for eighteen hundred red ones; an hour after his breakfast, which took place at eight o'clock, he found one white for seven hundred red globules; and, between eleven and one o'clock, the relative number of these plasmic cells had decreased again to one for fifteen hundred red globules. He dined at one o'clock; and soon afterwards the plasmic cells became more abun-

dant than they had been after breakfast, — one for about four hundred red globules. These experiments have been verified by other observers; nor would they have been given so fully, did they not seem to have an important bearing also upon that singular yet well-attested phenomenon, the gradual enlargement of the spleen during the process of digestion.

Thus Dr. William Dobson found this organ to be increased in size from the third up to the fifth hour after feeding; at which period it had attained its maximum, and afterwards began to diminish.

This active congestion and enlargement of the spleen during digestion is now a well-known phenomenon. Thus, indeed, are two widely separated and seemingly unimportant facts brought together in the close relation of cause and effect, and mutually made to corroborate each other. So, in the ever-varied book of Nature, are we tracing those wonderful relations in the phenomena which are constantly recurring around us. The fall of an apple suggests to a philosophical mind the law which gives harmony to the system of worlds. An occasional pebble thrown into the great ocean of thought leaves its ripple upon the sands; and the adventurer who comes afterwards sees in its impress the indications of some widely per-

vading law. Step by step, by the slow process of accretion, have all of the inductive sciences been built up. Thus, in a manner, has the knowledge of the physiology of the blood and the blood-making processes been acquired from widely separated and seemingly disconnected phenomena. Observation, in physiology, has taught but little; generalization, much. An age of observers has generally been followed by an age of theorists; but hardly ever, as in the case of Virchow, do we see the genius of the observer and the theorist combined. In the masterly manner with which he has handled not only the subject of leukæmia in all its bearings, but the whole theory of cellular pathology, we have a guaranty of the truth and the importance of his doctrines.

It is of the utmost necessity, in a discussion like this, to leave no step untaken which will lead to a more thorough knowledge of the facts upon which each author's views are, in a measure, based. As long ago, then, as 1847, the theory of Schwann, in regard to the animal cell, was somewhat modified by Virchow. As the matter then stood, what really appeared to constitute a vegetable cell, was the presence, within a non-nitrogenized membrane, of nitrogenized contents differing from it. Virchow has shown, that, in

all the essential constituents of animal cells, there are nitrogenized matters. But, in the lowest grade of animal cells, cartilage stands, in every respect, in the closest relation with vegetable tissue; and thus the ordinary membrane of the animal cell corresponds to the primordial utricle of the vegetable cell.

We have, then, in the primitive vegetable and animal cell, a structure of wonderful simplicity and constant recurrence in every living organism. There are certain laws, which it follows in its origin, development, and decay, which are necessary to it for its very existence. It is a vital entity of itself, whatever may be its position or its surroundings. Thus the blood-corpuscle enjoys a purely cellular existence. And as, according to Virchow, "all those cellular formations which lose their nuclei have a more transitory existence, they perish, they disappear, they die away, or break up;" so the red blood-corpuscle, which has already lost its nucleus, has run its appointed race, at least as a nucleated cell. Indeed, Virchow thinks there would be some doubts of the cellular nature of the red blood-corpuscle, were it not known to have a nucleus in the embryo.

The red blood-corpuscles are compared by him to

the uppermost cells of the cuticle, which have also lost their nuclei and are about to perish. Nothing could be more just than this comparison; since there is ample testimony to show that all embryonic blood, at least in the vertebrated series, abounds in corpuscles of an epithelial character and origin. Kölliker also admits of a complete identity between the earliest blood-globules and the histogenic cells of other parts of the embryo, and thinks that they are derived from the substance of the walls of the great vessels, as well as of the heart.

Remak has arrived at the same conclusion, and has demonstrated the presence of blood-globules in the great canals of the vascular area before the formation of the heart. The colored globules appear also at a very early period.

This epitheliated blood is found normally in all vertebrates in adult life, except the mammalia. Here it is found only in the embryo. This is one of those transitional stages, in which the morphological elements of the blood, during their progressive development, pass through many of the intermediate forms which become persistent in the lower classes of animals. Thus, in fishes, reptiles, and birds, the perfected blood-corpuscle is still only a nucleated cell,

identical with that of the human embryo, and of the embryonic state in other mammalia.

Another feature in his cell-doctrines has an important bearing upon his ideas concerning leukæmia and its origin. It is this, — that, in every physiological or pathological process by which a part grows or multiplies, the starting-points of these changes are in the nucleus; that there is no such thing as spontaneous cell-development; that, in all these processes, "an eternal law of *continuous development* prevails." Thus must every cell, whether it be a blood-corpuscle or a cartilage-corpuscle, have its origin from the nucleus of some anterior cell. This seems to be a general law which pervades all living organisms, and in accordance with which they attain the sum of their vital entities, and then perish in giving birth to other like structures. In regard to glands, he considers that their really active elements "are essentially of an epithelial nature." He thinks one of Remak's greatest merits was to have shown that the origin of these glandular structures is from the inner and outer of the three well-known layers of the germinal membrane, by the proliferation of their cells. He considers all glands as made up of these cells, and that their energies are spent in the development and transforma-

tion of them. He does not regard the blood as a permanent tissue, regenerating and propagating itself out of itself, but as constantly dependent upon other parts. Its elaboration, then, is the work of the cellular elements of the body, and its corpuscles are but so many floating glands. He has shown that every dyscrasia depends upon a permanent supply of noxious materials from certain sources. He then endeavors to determine what special influence the spleen or the liver exerts upon the composition of the blood. He concludes that certain organs bear a necessary, others only an accidental, relation to that fluid. Among the necessary ones must be reckoned the spleen and the lymphatic glands. He concludes, also, that the lymph conveys to the blood both substances from the tissues, and corpuscular elements from the lymphatic glands.

Leukæmia is an affection of these glands, having its origin in a numerical hypertrophy of their cellular elements.

In ordinary inflamatory diseases, it is rare to have the fibrine increased, without a multiplication, at the same time, of the colorless blood-corpuscles.

In leukæmia, Virchow thinks that the proportion of fibrine does not vary essentially; but that this is, in a measure, dependent upon circumstances.

Scherer has found in leucocythemic blood, hypoxanthine, leucine, uric, lactic, and formic acids; all of which occur normally in the spleen. The spleen, then, seems to be the principal organ at fault; although others of the lymphatic glands may give rise to leucocythemia. Virchow mentions an interesting case of acute hyperplasia of the bronchial glands, in which the blood was leukæmic. Nearly all the white blood-corpuscles in this instance contained but a single nucleus; the usual number being two, three, and even four nuclei.

According to this author, the same white blood-corpuscles may have one or many nuclei; one at an earlier, many at a later stage of development. Of this uni-nuclear variety of leucoythemic blood, a few cases have come under my own observation. Virchow thinks that the white corpuscles increase both in numbers, and perfection of development, the more the glands become enlarged which produce them. This fact has since been well established by Bennett, although the multiplication of white blood-corpuscles does not always keep exact pace with the degree of glandular hypertrophy. The size of the white corpuscles varies with their origin, and perhaps with the degree of glandular excitement. Those from the

spleen are the largest and most characteristic of leucocythemia; yet even these vary considerably in size and in the number of their nuclei.

In a case mentioned previously from Bennett, white blood-corpuscles of two distinct sizes were found in the same blood; the smaller ones being of the exact size of the nuclei of the larger, which they most probably were. A similar case is reported by Lebert; and his representations of them accord well with those of Bennett.

In conclusion, Virchow says, "*Irritation of the lymphatic glands explains, without any difficulty, the increase in the colorless, pus-like cells in the blood, and that, too, in all cases, — not only in those where pyæmia was expected to be found, but also in those where it was not expected, but where the blood, notwithstanding, exhibited the same quantity of colorless corpuscles as in genuine pyæmia answering to our clinical notions of the disease.*"

OBSERVATIONS IN UNITED STATES.

Since the discovery of leucocythemia, the attention of the medical profession of the United States has been directed to this subject by some very interesting and remarkable cases communicated to the various medical and surgical journals.

The following cases were under the most careful observation for several months; and the progress of the disease was watched up to the moment of its fatal termination. *Post-mortem* examinations were obtained; and the blood was examined microscopically, both during the disease and after death.

The following reports of these cases are very much condensed from the original communications. The first was communicated by Dr. Henry J. Bigelow to the Boston Society for Medical Improvement, November, 1858; and appeared in the Boston Medical and Surgical Journal, Feb. 2, 1860.

Case I. — A tall, well-formed man, æt. thirty-nine, had cough and poor health for six months, followed by sudden and painless enlargement of cervical, axillary, and inguinal glands. Cervical glands, and those in left axilla, slowly subsided while under treatment. During the summer, became anæmic, with occasional

epistaxis. In October, had intense hemicrania, lasting three or four days. Afterwards had herpes severely on lower part of body, and pleurisy in left side. Nov. 11, 1858, died of irritative fever, caused by spreading of herpes.

Autopsy by Dr. Calvin Ellis.

Head not examined. Pleuritic effusion in left side. Heart hypertrophied. Liver weighed seven pounds. Spleen was ten inches long, six broad, and four thick. Whitish deposit in kidneys and left suprarenal capsule, the same as in liver. Lumbar, iliac, and mesenteric glands enlarged.

Microscopic Examination.

Small granular corpuscles, or "globulins," found in coagula, .004 to .005 of a millimetre in diameter, and a few larger cells resembling the white corpuscles. The smaller corpuscles were identical with the nuclei of the larger, and found also in the enlarged organs. This case combines the splenic and lymphatic varieties of Virchow.

Case II. — Reported by Dr. Ellis (patient of Dr. Bowditch). Irishman, cigar-maker, æt. thirty-eight; entered the Massachusetts General Hospital, Novem-

ber, 1858. Ten weeks ago, first noticed enlargement of abdomen. Nausea after eating, lasting for a few weeks. Moderate appetite; bowels regular; occasional night-sweats; no fever or pain; some loss of strength, none of flesh; pulse ninety, and tongue natural; urine acid, specific gravity 1020, with some casts of tubuli and granular matter. During the last part of November (Boston Medical and Surgical Journal, Feb. 9, 1860), was more feeble, and lost appetite; became giddy, and deaf on left side. Dec. 4, began to have cough, followed in two or three days by muco-purulent, greenish, and bloody sputa, and many of the signs of pneumonia. Dec. 16, fell, and injured right brow. Delirious during the night, and died the next day.

Sectio Cadaveris (Dr. Ellis).

Some blood extravasated beneath the *dura mater*. Lower posterior part of right lung presented the appearance of pneumonia. Heart hypertrophied. Liver weighed six pounds and four ounces, and the spleen nearly five pounds. Lymphatic glands along the trachea enlarged. Kidneys pale, and weighed seven and a half ounces each. The blood showed *a great preponderance of the white corpuscles*.

They contained either single granular nuclei, .005 of a millimetre in diameter, or two or three smaller globules arranged in the form of a semicircle. Similar corpuscles were found in the lymphatic glands, with free nuclei, or "globulins," similar to the included ones. In specimens of this blood, Dr. White found numerous minute crystals. They were colorless, elongated, faintly marked, rhombic octahedra, exhibiting irregularities of form indicating an organic nature. To these crystals he has given the appropriate name of "Leukosin."

Case III. — Read before the Boston Society for Medical Improvement, Nov. 11, 1861, by Calvin Ellis, M.D. (patient of Dr. Storer).

Female, æt. fifty-five years; anæmic, never menstruated nor had hemorrhage. Subject to dyspepsia and neuralgia. During the last year of life, complained of pain and fulness in abdomen. Liver thought to be enlarged. Died of exhaustion in May. Spleen three or four times the usual size. Liver enlarged also. Other organs healthy.

Case IV. — *Patient of Dr. Dupee.*

Provision-dealer, æt. twenty-four years; very muscular. Had a severe blow over stomach eighteen months before death. Six months afterwards, in the

summer of 1860, was treated for dyspepsia. Two months before death, enlargement of the spleen was first noticed. No pain or tenderness. Frequent headache and dizziness, and occasional epistaxis. Anæmic; no dropsy. Lymphatic glands not enlarged. Slight cough in winter. Appetite ravenous. Bowels regular. Lost flesh and strength, and died July 10, 1861.

Autopsy five hours after death (Dr. Ellis).

Face livid, abdomen tense, lungs healthy, heart enlarged. Liver weighed thirteen and a half pounds; and the spleen, nine pounds. Kidneys, lumbar, and mesenteric glands, enlarged. No change in Peyer's glands. Blood composed almost entirely of white granular corpuscles, containing single nuclei. Nearly two days after death, crystals were found in the blood. These crystals were examined in both cases by Dr. White; and they were found to be similar in this case to those previously discovered by him.

As they were not found until some time after death, it is probable that they were due to some *post-mortem* change. Similar crystals were subsequently found in leucocythemic blood by some of the Continental observers.

We have in these cases good illustrations of the lymphatic and splenic varieties of leucocythemia. In all of them, there was a great abundance of the blood globulins; and, some time after death, of peculiar microscopic crystals* of an organic nature. The cause of this excessive multiplication of the blood-globulins remains to be considered.

LEBERT.

The following characteristic examples of leucocythemia we have translated almost literally from Lebert's great work on pathological anatomy, "Traité d'Anatomie Pathologique, Générale et Spéciale," published at Paris in 1857.

Their histories bear a striking resemblance in their general outline to those of the cases already quoted. All of these patients were but little benefited by treatment, and for a time only; the disease progressing steadily towards its fatal termination.

Case I. — I saw the patient who was the subject of this observation, in the service of M. Rayer, where M. Leudet has collected the details of it, which he has published in the seventh volume of "Mémoires de la Société de Biologie."

A woman aged thirty years, seamstress, small, pale,

* Except the first, where they were not looked for.

and meagre ; had been regular in her courses since fifteen years of age. She has had no other disease except the varioloid since twenty-six years of age. Two years and a half ago, she had a child. She has lived in good hygienic circumstances ; but her husband has often maltreated her. She has never had intermittent fever. The patient dated her actual disease back two years and a half. Already, during her pregnancy, she had spells of dizziness. About two or three weeks after her confinement, which had been a happy one, she perceived a hard but indolent tumor below the false ribs of the left side. In two months, this swelling had acquired a considerable volume. The patient had experienced weighty pains during the prolonged course, and shortness of breath on going up stairs. She continued to work until the end of 1851 ; but already, for some months, she had seen her strength and her flesh diminish. She had night sweats and a slight cough.

In January, 1852, she passes three weeks in a hospital, where she is treated with sulphate of quinine and the preparations of iron. She experiences little change, and leaves. Soon she perceives her left inferior extremity tumefy, commencing at the groin. She experiences darting pains in the popliteal space.

Feb. 27, she entered the hospital of La Charité, in the service of M. Rayer. There is shown to exist, besides the very considerable volume of the belly, an enormous tumefaction of the spleen, which extends from the anterior superior spinous process of the ilium to within two fingers' breadth of the left breast. The tumor extends beyond the umbilicus. Its surface is smooth, its consistence firm. The liver is tumefied in the left lobe. The belly is meteorized. The patient has alternately constipation and diarrhœa. She coughs a little; her voice is raucous; she has frequent palpitations; a souffle is perceived for the first time; pulse small, 96; night-sweats abundant. Absence of physical signs of pulmonary tubercles; œdema of left inferior extremity. The patient gradually becomes more feeble. In the month of April, the diarrhœa becomes abundant; she loses appetite, and dies of marasmus on the 12th of April, about twenty-two months after the commencement.

The treatment has consisted in the employment of the waters of Vichy,* lemonade for drink, a nourishing diet, and finally, against the diarrhœa, in the use of opium in clysters, and of gummed rice-water as a ptisan.

* Acid, resembling Seltzer in composition.

Autopsy twenty-three hours after death.

The blood taken from the heart and great veins is of a pale brown, of the color of clear chocolate; no part blackish or well coagulated. Its consistence is rather creamy: it contains points and little clots of the volume of a pea, and of a whitish color. In examining the blood with a microscope, proportionably very few red globules are found: there are at least three-quarters, if not more, white globules. The latter are larger, more developed, than in the normal state. They are one-eightieth of a millimetre in diameter. Several of them approach the oval form. Their nuclei exceed, in general, one two-hundredth of a millimetre; and, in many of them, nucleoli are seen, which are so rarely distinguished in the ordinary white globules. The abdomen contained only about half a pint of a citrine serum.

The spleen is thirty centimetres (eleven and eight-tenths inches) in length. Its capsule is thickened in many parts, and attached by cellular adhesions to the diaphragm, and even to the surface of the colon. Its circumference, in its great diameter, is sixty-four centimetres (twenty-five and two-tenths inches); in its small diameter, thirty-eight centimetres (fourteen

and nine-tenths inches). Its consistence is firm, and very nearly that of raw ham; its color, of a deep reddish-brown. The liver is equally augmented in volume, of a firm consistence and normal structure. The lymphatic glands, at the passage of the inferior vena cava through the diaphragm, are enlarged; the mucous membrane of the large intestine is red and softened; all the other organs are healthy.

Case II. — A little while after I had observed this case at La Charité, I saw a similar one in my private practice. M. de L——, aged thirty-two years, of a delicate constitution, has never had any severe sickness; but for many years has been subject to hypochondria, and to a most obstinate constipation. In 1851, I had ascertained a slight engorgement of the liver, and submitted the patient to a treatment by the waters of Vichy. A sensible improvement took place in his whole health.

In January, 1852, I took care of him for an acute articular rheumatism, which was confined to the left coxo-femoral articulation, and of which he was soon cured. At the commencement of May, he consulted me anew for his constipation, which had become very obstinate, accompanied by a hypochondria still more pronounced than usual, diminution of appetite, a

general *malaise*, and increasing loss of strength. Upon palpation, I determined that the liver extended below the false ribs, to the breadth of three fingers; that it passed a little beyond the median line; and that pressure, without being painful, occasioned discomfort. But I was much more painfully surprised, when, examining the spleen, I found the latter at least triple in volume, extending beyond the false ribs of the left side by a good hand's-breadth, and upwards, within two breadths of the finger below the nipple. It was painful on pressure. The most attentive inquiry gave me the conviction, that the patient had never had intermittent fever. The belly was swollen and bulged out; the patient could no longer button his pantaloons; his appetite was almost nothing; his constipation of the most obstinate character. He passed, only once in three or four days, hard and dry matters; his color was pale and earthy. It was easy for me, from that time, to diagnosticate this form of hypertrophy of the spleen, which, independent of all intermittent fever, constantly accompanies leukæmia; although I had not had occasion to verify this last fact in the actual case. Knowing already how powerless therapeutics were in such cases, I wished to try a means which enjoyed a great reputa-

tion in the resolvent treatment of visceral engorgements. I sent the patient to the waters of Karlsbad, in Bohemia.

During this sojourn, which lasted six weeks, his bowels became regulated, his strength and appetite returned a little, and he was momentarily better. But a new and alarming symptom declared itself: œdema of both legs came on, which happily soon disappeared. In the month of July, the patient returned to Paris, calling himself better, and feeling better; but, unhappily, not being so at all. The tumefaction of the abdomen had augmented, and the spleen descended four centimetres (an inch and a half) lower than at the moment of departure. In front, it had attained the median line. During the three months following, the patient was successively submitted to a treatment by the waters of Vichy; to the use of the iodide of potassium, in the dose of twenty-five to thirty centigrammes (four to five grains nearly) daily in a bitter infusion; to iodurated frictions upon the abdomen; and, later, to the ferruginous preparations, the iodide of iron, the lactate of iron, &c.

The constipation was combated by injections of cold water, small doses of calomel, pills of aloes and rhubarb, &c. A substantial diet was prescribed dur-

ing all this time. Notwithstanding this active treatment, nothing arrested the disease in its rapid march. The engorgement of the spleen made incessant progress: it soon attained the iliac region, ascended above on a level with the nipple, and extended in front beyond the umbilicus.

The liver neither augmented nor diminished in volume. The appetite was irregular; the bowels remained sufficiently regular, thanks to the medicines: but the patient was a prey to discouragement and sadness. The enormous volume of his abdomen gave him an air of discomfort, and occasioned him an increasing oppression. He fell rapidly into marasmus: no ascites supervened. During the last days only, the œdema of the inferior extremities re-appeared; and, at last, a double hydrothorax terminated the days of the patient, the 31st of October, 1852. During the last month, the constipation had given place to a slight diarrhœa. At no time did he have hemorrhage.

Case III. — It is probable that leukæmia exists sometimes in a slight degree, without giving rise to characteristic symptoms. Very recently, a man succumbed in my division, at the hospital *de Zurich*, to a pulmonary tuberculosis, rapidly coming on after the extirpation of a scrofulous testicle, which had been

done a short time after his entrance, two months before his death. He presented above the right knee a considerable hemorrhagic effusion, which struck me by its color, of a yellowish-red, and for which the microscopical examination demonstrated an indubitable excess of the white globules of the blood in relation to the red ones.

Before closing this essay, we will briefly review the ground which we have gone over; giving any new facts which may have become known to us during these investigations.

Although it has been asserted that Malpighi was the discoverer of the blood-corpuscles, little, however, was known of their existence before 1673, when Leeuwenhoek, with microscopes of his own construction, first saw them distinctly in the human blood. He soon extended his inquiries to that of different animals, and arrived at the important conclusion, that the color of the blood is due to the presence of these corpuscles; and that, in birds, frogs, and fishes, they are oval disks.

Nearly a century passed away without any thing additional being known concerning these elements of the blood. But, in 1770, Hewson commenced the

publication of a series of observations upon the contents of this fluid; which, for their accuracy, have served as the basis of the physical history of the blood.

A half-century elapsed without any material advancement being made in these interesting inquiries. But this period of mental repose was destined to be followed by one of greater activity than any before. The perfection of the miscroscope by Amici of Modena, and Lister in England, gave a new impulse to these investigations. The number of good observers had increased, and their attention was soon drawn to the study of the blood-corpuscle, in its different phases of development; and several new theories concerning it were advanced. Among them, that of Wharton Jones, who considers the red blood-corpuscle "*a free cellæform nucleus*," is supported by the best authorities at the present day. The functions of the lymphatic glands had long before been ably demonstrated by Hewson, and their minute anatomy attentively studied and described. In 1836, Schultz had made some important observations in regard to the mode of origin and development of the blood-corpuscle, which coincided with the views previously entertained by Hewson. Two years later, the scientific world was

made acquainted with the beautiful theory of Schleiden in regard to the formation of the vegetable cell. The next year, the theory of Schwann, in regard to the animal cell, was published.

Thus a new impulse was given to the study of vegetable and animal physiology, which has resulted in some of the most important discoveries in the annals of physiological science. Some of these views have been modified, in a measure, by Virchow, Hugo von Mohl, Braun, and Kölliker; and the study of leucocythemia has not been without its influence upon our ideas of the origin and development of animal cells.

But little attention had been given since the time of Hewson to the study of the blood-making organs, until the year 1832, when Sir Astley Cooper published his admirable essay upon the "Anatomy of the Thymus Gland." This event formed a new era in the study of these organs. The works of Gerber, Müller, Nasse, and others, soon made important accessions to what was already known of the various ductless glands.

The thymus, thyroid, and spleen were soon associated together under the common name of blood-glands.

The liver has also had a place assigned to it in the blood-making processes; and it probably performs this function largely during fœtal existence. The glands of Peyer have lately been shown by Professor W. His, in an article in the "Annales des Sciences Naturelles," Paris, 1862, to be also intimately concerned in the production of the blood-corpuscles.

We will translate a few extracts from his interesting and valuable paper. He says, "The glands of Peyer and the isolated follicles of the intestine are not peculiar formations: they must be regarded as a very considerable mass of adenoid substance." And he also says, "The fundamental tissue of the intestinal mucous membrane, which has thus far been regarded simply as connective tissue, is formed by a substance which possesses the essential properties of the substance of the lymphatic glands; and which, for this reason, we place in the same rank as this latter, in giving to it the name of *adenoid substance*." Furthermore he says, "For myself, I do not hesitate to admit, that the whole adenoid substance of the intestine, that of the follicles as well as that of the parenchyma of the villosities and of the interglandular tissue, may concur in the formation of the blood-corpuscles; that is to say, that the cells accumulated

in this substance are not destined to remain there, but to pass at first into the chyliferous ways, and thence into the torrent of the circulation."

In conclusion, he says, "However it may be, and notwithstanding all objections, we cannot deny that the adenoid substance plays a part in the formation of the blood-cells. When we see always masses of colorless cells carried by the lymph into the blood; when we have no reason to believe that these cells are formed in the vessels themselves; when we meet, in many parts of the body, organs which contain, in great quantity, cells perfectly similar to the lymphatic cells, and which are found in conditions the most favorable for the ulterior multiplication of these cells, — it is well permitted us to suppose that these latter pass from these organs into the blood. This supposition acquires still more appearance of truth, when we consider the relations of the lymphatic vessels with the organs in question. The latter, in fine, which we unite under the common denomination of adenoid organs, have, at the same time, afferent and efferent lymphatic vessels, or only efferent vessels. In the latter case, these vessels contain always a quantity relatively more considerable of colorless cells: in the first case, it is still in the efferent vessels

that the colorless cells are found in the greatest number.

"Let us add to this, that the adenoid organs are found tumefied when there is observed an augmentation in the production of the colorless blood-cells; that they are altered pathologically in diseases of the blood; and, in fine, that the cells which they contain have not at all the characteristics of stable cells, since they offer, on the contrary, all the attributes proper to young cells, — a rounded form, a granular aspect, a cellular membrane closely adhering to the nucleus, &c. Wherever we find similar cells, we see them undergo ulterior metamorphoses.

"Of late years, we have seen many organs ranged in the series of adenoid organs. It is necessary to try to render this series complete by finding their analogues in all parts of the body which furnish the lymph carrying cells. It is known that these latter are not always met with in the lymph: that of the liver, for example, is an instance, as Kölliker showed, a long time ago, and I have confirmed. I also found the lymph of the thyroid gland of cats exempt from cells. According to Teichmann, these latter exist in the lymph of the extremities before this lymph has traversed the lymphatic glands. There is still room

for finding here the adenoid organs, either in the skin or in the tunics of the articulations."

Having said thus much in relation to the adenoid or glandular organs, it will be proper here to give some account of the corpuscular elements which they furnish to the circulating fluid. These corpuscles have been studied attentively by Müller, Donné, Milne Edwards, Gulliver, and others; and to them has been given the name of *plasmic cells*. As commonly found in the blood, they consist of two distinct varieties, — the *white globules* and the *globulins*. The former are familiar to every observer; and, in man, their usual diameter is about the one-hundredth of a millimetre; whilst that of the globulins scarcely attains the one three-hundredth of a millimetre.

Some of these white corpuscles contain one nucleus, others several nuclei. The larger and more developed they become, the less granular are they; and, under these circumstances, their nuclei can often be distinctly seen, without the addition of acetic acid.

Gulliver has mentioned several kinds of corpuscles as having been found in the efferent lymphatics of the different blood-glands. In the chyle, he found albuminous granules and scarcely colored lymph-corpuscles, or young blood-cells; the latter increasing in number,

size, and color, on approaching the thoracic duct. The following elements, with their dimensions, have been found in the chyle of mammals: —

A. — White globules, average diameter, $\frac{1}{2800}$ of an inch.
B. — Lymph „ „ „ $\frac{1}{4000}$ „ „
C. — Minute spherules, „ $\frac{1}{3000}$ to $\frac{1}{1000}$ „ „
D. — Blood-corpuscles seen by Schmidt, Schultz, Gurlt, &c.
E. — Oil-globules, very variable in size.

The latter were only twice seen in considerable numbers in the human chyle. In addition to these plasmic elements, we find others having their origin in the thymus, liver, spleen, and supra-renal glands. The corpuscles from the liver are three times as large as those from the spleen, and contain spherules one fifty-three hundredths of an inch in diameter. The corpuscles of the spleen vary in diameter from one six-thousandth to one seventeen-hundredth of an inch; their average being one three-thousandth of an inch. Thus their average size is about that of the red blood-corpuscle. In addition to these, Kölliker has described what he terms "corpuscle-holding cells" existing in the spleen, and containing from one to twenty blood-corpuscles; these latter gradually becoming less in size, and of a yellow, brownish red, or even black appearance, and finally breaking up

into pigment granules and pigmented granule-cells, which gradually lose their color.

In the liver of the embryo, he has also found oval and elongated cells with two nuclei; these cells being in the process of multiplication by division. All of the above corpuscles are found in healthy blood.

Milne Edwards mentions several species of globules found in pathological conditions of the organism. Some of these are identical with those before mentioned. They are as follows: —

1. Cells or spherules which contain one or many red blood-globules, in general more or less altered, and which have been observed in the spleen, the liver, &c., by Ecker, Kölliker, Gerlach, Sanderson, and several other physiologists.

2. Granulated pigmentary cells, described by Kölliker, Ecker, H. Meckel, Virchow, Funke, &c., and found principally in those attacked by intermittent fevers, and affections of the spleen.

3. Spherules or collections of finely granulated matter, observed in the blood of the splenic vein by Funke.

4. Corpuscles with concentric layers, three or four times larger than the ordinary white globules, similar to those of the thymus, and found by Hassal in a fibrinous clot of the heart.

5. Cells similar to pus-corpuscles, and with a single nucleus. They are found mingled with a great many free nuclei, and have been observed in abundance in persons affected with tumefaction of the spleen or the lymphatic ganglia.

6. Pale, granulated, or pigmentary cells, which are provided with caudiform prolongations, and which have been described by Virchow, Cowan, &c.

Having spoken of the blood, the blood-making organs, and of the various kinds of corpuscles which are found in the circulating fluid, both in health and in disease, we will now consider some of the more intimate relations which these hold with leucocythemia.

There are two distinct theories now entertained in regard to the mode of origin of the blood-corpuscles. The first is, that they are of an epithelial origin, and are only the transformed nuclei of the cells of the lymphatic glands.

The second theory is, that they originate in the circulating fluids by mere molecular aggregation. The former is the theory of Wharton Jones, Burnett, Virchow, and of the cellular pathologists generally. They look upon the blood-cells as utricles with or without nuclei, according to the particular stage of

their growth: the younger ones containing them; the older, not. They consider that the power of self-multiplication resides in the cells themselves, and not in the molecular fluids by which they are surrounded, and which only serve as materials for these changes. The molecular theory of cell-origin, of which Bennett is the most eminent expounder, is elaborately set forth in his late lectures upon this subject. We will quote a portion of a paragraph from his fifth lecture, in which he most clearly defines his views.

In speaking of chylification and sanguification, he says, "The glands of Peyer I agree with Brücke in considering as the first series of lymphatic glands. These are succeeded by other series in the mesentery. All of them are connected with one another by lacteals, which ultimately terminate in the thoracic duct. They serve to subject the molecular chyle, as it is first derived from the chyme, to the action of these glands. Here the onward flow of the fluid is somewhat delayed: an exchange takes place between it and the surrounding blood, and nuclei and cells are formed — more especially, however, nuclei — by molecular aggregation.

"It is clear, therefore," says he, "that chylification and sanguification are perfected through the action of

the lymphatic glands upon the molecular chyle; that in them the blood-corpuscles are formed, and conveyed by the thoracic duct into the circulation, at a point not far from the right side of the heart; from thence they are rapidly propelled into the lungs, where, on being exposed to the oxygen of the atmosphere, they assume color, and thereby become the colored corpuscles of the blood."

In opposition to this tendency towards the molecular theory in physiology, Milne Edwards long ago clearly expressed himself. He thinks that the best established facts seem to show that the blood-globules "are not simple inert concretions of animal matter, resulting from a kind of precipitation or spheroidal coagulation; that these are, on the contrary, living parts, utricles which increase and become modified in their structure by the progress of age, which are the seat of physiological phenomena, and which ought to be considered as so many little organs endowed with a kind of special activity."

In speaking of growth and secretion, Bennett fully admits, that, while the blood is transformed into tissues and secretions, it cannot be attributed to any power residing in the blood or blood-vessels, but that the attractive and selective powers of the economy are

seated in the tissues themselves. Thus the lines of separation between the molecular theory of Bennett and the cellular theory of Virchow are far from being so distinct as they were at first supposed to be.

The temporary increase of white corpuscles in the blood, denominated by Virchow, *leucocytosis*, has been well confirmed by numerous and careful observers.

The splenic and lymphatic varieties of leucocythemia mentioned by this author have also their foundations in nature, and are characterized by different kinds of white corpuscles. Those originating from the splenic variety are large and well-developed cells with one or more nuclei, and resemble very much the constituent elements of the spleen itself; whilst those from the lymphatic variety are generally small, with large, single, sharply-defined nuclei, with dark outlines, and a somewhat granular appearance.

His idea that lukæmia is a kind of permanent, progressive leucocytosis, clearly separates a pathological from a physiological condition. He thinks that the morphological elements of the blood are formed by the spleen and the lymphatic glands, and that these elements are the real descendants of the cellular bodies of these glands, which have been set free in

their interior, and conveyed into the blood. He speaks of the fatal results in nearly all of the well-marked cases of this disease, and of the exhausting hemorrhages in the form of epistaxis, and occasionally of melæna, which usually occur towards the close of life. He mentions a few diseases in which an unusual number of these white corpuscles are found; such as puerperal and typhoid fevers, and sometimes pneumonia. He speaks also of their occurrence during advanced gestation. What causes this numerical hypertrophy of these glandular organs is as yet unexplained: it doubtless depends upon something which affects the nutrition of their cellular elements. Whether this change is due to vital or physical influences is at present wholly unknown to us.

Although much light has been thrown upon the nature of this disease by the writings of Bennett, we are still, in a great measure, indebted to Virchow for his calm, careful, philosophical view of the whole subject. His ideas of the blood, and its relations to the economy, have an important bearing upon the study of this disease. He does not consider the blood, as many do, a permanent tissue, regenerating itself out of itself, but as dependent upon the other tissues, receiving its corpuscular elements from them, and

giving to them, in return, the materials for new growth. The blood then holds in solution the living and dead materials of the system; and its condition is therefore, in a measure, dependent upon that of the tissues themselves, and its corpuscular elements are derived from that source. Leucocythemia is a disease of the blood-making tissues, although its most prominent characteristics are found in the blood itself.

There is something wonderful in the mutual relation between the blood, which is the life of the tissues, and the tissues, which are the life of the blood. It is but another example of that perfect Wisdom, which knows of no limit in the infinite variety and beauty of its designs.

Let us, then, while we regard the high offices which the tissues perform for the circulating fluid, be not unmindful of that prophetic saying of Holy Writ: "*The life of the flesh is in the blood.*"

AUTHOR'S CASES.

Case I. — (See page 95, plate.) March 31, 1863. John S——, aged eight years. Has dark hair and eyes, and a good complexion, but somewhat anæmic lately. About two months ago, he came under treatment for hypertrophy of the cervical lymphatics, which had commenced about ten months previous. His health at this time had not apparently suffered much from this source. His blood was found to contain numerous white corpuscles, — from ten to fifty times as many as are usually found in perfect health. He was then attending school, and has continued to do so up to the present time. There was no pain in this enlargement at that time; nor had there been any of consequence since it was first noticed. Within the last two months, the tumor has steadily increased in size, until it is now nearly double the volume it was then. Lately he has been subject to headache; probably from pressure upon the recurrent vessels of the neck. He is able to walk two or three miles without being much fatigued, although his motions are somewhat constrained by the firm manner in which his neck is held by the enormous mass which partly encircles it. This mass begins to press upon the trachea,

and slightly interferes with the respiration when it is much hurried from bodily exertion. Upon palpation, the tumor appears to be lobulated; many of the lobules being, to some extent, movable. Those towards the trachea seem to be more adherent than the others. Upon consultation, it was decided that the tumor had better be removed. The operation was performed by Dr. Cheever. It was a very tedious, not to say difficult one; and the little patient appears to be quite comfortable after it.

From examination thus far, the tumor appears to consist of a lobulated mass of hypertrophied lymphatic glands, firmly bound together by investing fibrous tissue.

MICROSCOPIC EXAMINATION.

Microscopic examination of scrapings from the cut surface of the glandular substance shows it to be densely crowded with both the red and white corpuscles of the blood. Numerous globulins are also found, some in the interior of the white corpuscles, and contrasting with them by their faint yellow appearance. The white corpuscles have a distinct outline, and are nearly circular. They have a smooth surface, are not granulated like those of pus, and are nearly of the size of the ordinary red blood-corpuscle.

The globulins were about a quarter to a third of the diameter of the red blood-corpuscles. The examinations were made with Spencer's objectives, with powers of two and four hundred diameters. The venous blood from the gland contained a large number of similar corpuscles. No evidence was given of pus by the addition of acetic acid. The same results were obtained from a microscopic examination made by Dr. Cheever.

April 1, six, A.M. — The patient is very comfortable, and there has been no hemorrhage from the wound.

Case II. — Feb. 9, 1863. J— D—, aged twelve years the 30th of June last. (See p. 96, plate.) His mother died of fever; his father is living. The boy has dark hair and eyes, an intelligent and thoughtful countenance, and a somewhat anxious and sad expression at times. Five years ago, he had measles or scarlet fever; and has been more or less pale ever since. During the last two years, has been in poor health. Generally constipated. Three months ago, had ascites, and œdema of the legs, lasting about six weeks; for which he was treated, and entirely recovered. He had, at the same time, a slight cough, which gradually disappeared with the ascites. His

appetite and digestion are both good. He is very fond of milk, of which he drinks a considerable quantity. Sweats some at night, and has lost some strength, but no flesh. No trouble of heart. Hypertrophy of liver and spleen. Respiration at apex of left lung somewhat rude. Percussion of chest about normal. Is able to attend school. March 28. — Is now suffering from ascites, and œdema of legs. There are two distinct enlargements of the abdomen, — the upper at the margin of the false ribs, and which is due to the hypertrophy of the liver, &c.; the lower, beneath the umbilicus, and caused by the ascites. A distinct sulcus separates the two. There is a slight vesicular eruption upon the legs, probably caused by the œdema. During the last few months, the blood has been leucocythemic. Besides the white blood-corpuscles, quite a variety in the form of the red ones has been observed. Globulins were very numerous: some of these were united in pairs, in the form of dumb-bells. During the past week or two, he has suffered from the increased œdema of legs, — a thin, serous fluid constantly trickles from them; yet he bears his sufferings patiently, and without a murmur. What his prospects of life are, under these circumstances, is a matter of not very difficult prognosis.

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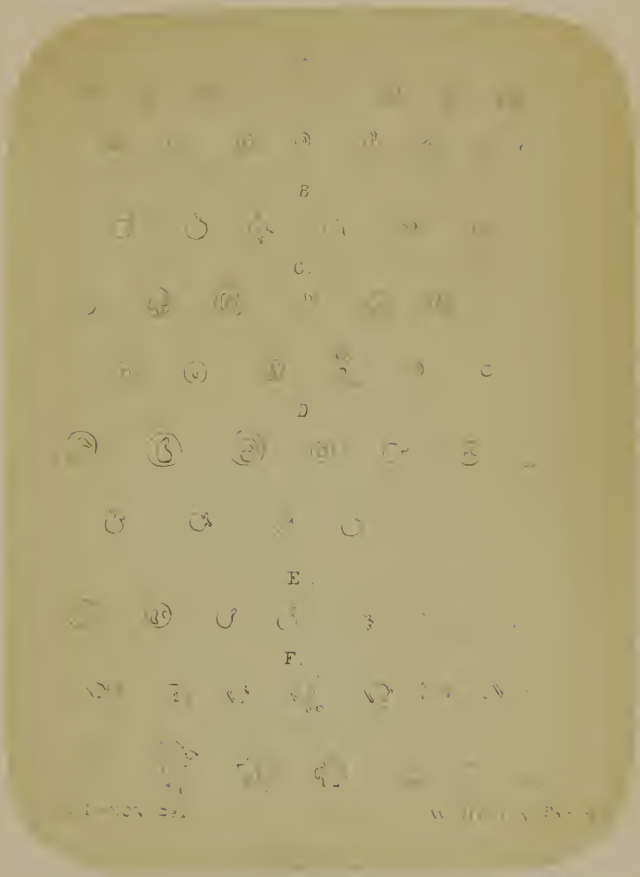
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